UCB, Inc. - 1950 Lake Park Drive, Smyrna, Georgia 30080

April 7, 2009

Roger Citron
State of Montana Medicaid

Dear Mr. Citron:

Your UCB, Inc. Representative Bobby White contacted the Medical Affairs Department with your request for information regarding Vimpat® Tablets (Lacosamide) and Vimpat® Injection (Lacosamide). Thank you for letting us know how we can assist you.

Specifically, you requested:
• Information regarding use in epilepsy overview (attached)
• Information regarding SP667 - Pivotal Trial (attached)
• Information regarding SP754 - Pivotal Trial (attached)
• Information regarding SP755 - Pivotal Study (attached)
• Information regarding open-label extension trial (attached)
• Information regarding adverse reactions and safety (attached)
• Information regarding clinical trials (attached)

VIMPAT® (lacosamide) tablets are indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older. [1]

VIMPAT® (lacosamide) injection for intravenous use is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older when oral administration is temporarily not feasible. [1]

This material is provided in response to your specific request and may contain information that is not part of the FDA-approved product labeling. If you have additional questions or a patient has experienced an adverse event related to the abovementioned product(s), please contact us toll free at (866) 822-0068, option 9: Medical Information. We appreciate your interest in UCB, Inc., and in our products.

Sincerely,

Joanne Chia
Medical Information Specialist

US-JCH/JCC/4109

Enclosure(s):
Vimpat® Package Insert

VIMPAT® (lacosamide): Overview – Clinical Use in Epilepsy

SUMMARY:

- The efficacy and safety of oral VIMPAT® (lacosamide) (LCM) has been studied in approximately 1300 patients in 3 randomized, double-blind, placebo-controlled pivotal trials as adjunctive use in patients with uncontrolled partial onset seizures who are already using 1 to 3 approved concomitant anti-epileptic drugs (AEDs).[2-5]
- In all 3 trials, the primary efficacy endpoints were the median percent reduction in seizure frequency over placebo per 28 days from Baseline to Maintenance Phase and the 50% responder rates. [2-5]
    - For all trials, the LCM 400 mg/day dose was statistically significant for both endpoints. [2-5]
    - In SP755, LCM 200 mg/day demonstrated statistically significant reduction in seizure frequency over placebo ($p < 0.05$). [4]
    - In SP667 and SP754, the LCM 600 mg/day doses demonstrated statistically significant results for both primary endpoints. [2-3]
- In a post-hoc pooled analysis of the pivotal trials, 84% of included patients were uncontrolled despite treatment with two to three AEDs. [5]
- The baseline seizure rate was high, with subjects reporting more than 2 to 3 times the number of seizures required by the inclusion criteria. Baseline rates ranged from 9.9 to 16.5 seizures per 28 days. [2-5]
- The most frequent (≥10%) treatment-emergent adverse events were central nervous system- and gastrointestinal-related events. [2-5]
- LCM had no clinically relevant influence on ECG, laboratory values, vital signs or body weight; however, a small, dose-related increase in PR interval was observed. [2-5]

The package insert for VIMPAT® (lacosamide) (LCM) contains information in the CLINICAL STUDIES and ADVERSE REACTIONS sections on this topic. Please review the enclosed full prescribing information.[1]

PARTIAL ONSET SEIZURE PIVOTAL TRIALS [2-5]

i. Overview of SP667, SP754, and SP755

Efficacy

The efficacy and safety of adjunctive oral VIMPAT® (lacosamide) (LCM) in patients with uncontrolled partial seizures was evaluated in three randomized, double-blind, placebo-controlled studies (SP667, SP754, SP755). [1-3] Patients were randomized in a fixed, forced titration scheme to either placebo, LCM 200 mg/day, 400 mg/day, or 600 mg/day (SP667); to placebo, LCM 400 mg/day, or 600 mg/day (SP754); or to placebo, LCM 200 mg/day, or 400 mg/day (SP755; BID dosing for all LCM treatments). Eligible patients had at least 8 partial seizures (4 for SP667) during an 8-week baseline period, with no more than a 21-day seizure-free period. Concomitant antiepileptic drugs (AEDs) were kept stable in subjects with or without additional vagal nerve stimulation (VNS). Titration occurred over 6 weeks (4 weeks

for SP755) in 100 mg/week increments, and patients were maintained at their randomized dosage for 12 weeks. After the 12-week maintenance phase, patients underwent either a 2 week transition into an open-label extension trial or a 3 week taper off trial medication (SP667,SP754). Patients enrolled in SP755 underwent a 2 week transition or taper after the maintenance phase.

Table 1: Summary of Pivotal Trial Designs [2-5]

Lacosamide Trial	Ben-Menachem [2] (SP667)	Chung [3] (SP754)	Halász [4] (SP755)
Phase	II	III	III
Total Randomized	n = 418	n = 405	n = 485
Age, years	18-65	16-70	16-70
Treatment Group, mg/day	PBO LCM 200, 400 and 600 mg/day	PBO LCM 400 and 600 mg/day	PBO LCM 200 and 400 mg/day
Duration			
Baseline	8 wk	8 wk	8 wk
Titration	6 wk	6 wk	4 wk
Maintenance	12 wk	12 wk	12 wk
Number of concomitant AEDs	1–2	1–3	1–3

LCM was associated with significant decreases in seizure reduction during the maintenance phase, versus placebo (Table 1). At dosages of 400 mg/day and 600 mg/day, median seizure reduction ranged from 36% to 40%. A similar pattern was observed for responder rate (defined as a ≥50% reduction in POS frequency per 28 days from baseline), as the 400 mg/day and 600 mg/day dosages were associated with significantly higher rates than placebo. LCM 200 mg/d significantly reduced seizure frequency in one study (SP755). The responder rate for LCM 200 mg/day was greater versus placebo but did not meet statistical significance.

Table 2: Efficacy outcomes in lacosamide studies SP667, SP754, and SP755 (FAS). [2-5]

Study	n (efficacy analysis)	Median Percent Reduction in Seizure Frequency per 28 days (p-value vs. placebo) †	Responder Rate (≥50% reduction) (p-value vs. placebo)	Seizure Freedom during maintenance phase n (%)
SP667				
Placebo	96	10%	22%	0
LCM 200 mg/day	107	26%	33%	1 (1%)
LCM 400 mg/day	107	39% **	41%**	5 (6%)
LCM 600 mg/day	105	40% **	38%*	1(2%)
SP754				
Placebo	104	21%	18%	0
LCM 400 mg/day	201	37%**	38%**	4 (3%)
LCM 600 mg/day	97	38%**	41%**	5 (8%)
SP755				
Placebo	159	21%	26%	3 (2%)
LCM 200 mg/day	160	35%*	35%	5 (4%)

LCM 400 mg/day	158	36%*	41%**	3 (2%)

* p <0.05, ** p < 0.01, FAS - Full Analysis Set (All randomized subjects receiving ≥ 1 dose of trial medication with ≥ 1 post-baseline efficacy assessment)
† p-values reflect the percent reduction over placebo and are based on log-transformed data from pairwise treatment ANCOVA models

Table 3: Efficacy outcomes in lacosamide studies SP667, SP754, and SP755 (PPS). [2-5]

Study	n (efficacy analysis)	Median Percent Reduction in Seizure Frequency per 28 days (p-value vs. placebo)†	Responder Rate (≥50% reduction) (p-value vs. placebo)	Seizure Freedom during maintenance phase n (%)
SP667				
Placebo	85	12%	21%	0
LCM 200 mg/day	84	33%*	38%*	1 (1%)
LCM 400 mg/day	79	46%**	49%**	5 (6%)
LCM 600 mg/day	63	49%**	49%**	1 (2%)
SP754				
Placebo	87	22%	18%	0
LCM 400 mg/day	140	40%*	40%**	4 (3%)
LCM 600 mg/day	53	50%**	51%**	4 (9%)
SP755				
Placebo	138	25%	28%	3 (2%)
LCM 200 mg/day	140	35%*	35%	5 (4%)
LCM 400 mg/day	121	45%*	46%**	3 (3%)

*p <0.05, ** p < 0.01, PPS – Pre Protocol Set – Patients with ≥ 1 seizure-frequency assessment collected during the Maintenance Phase with no major protocol deviations
† p-values reflect the percent reduction over placebo and are based on log-transformed data from pairwise treatment ANCOVA models

Safety

The most frequent (≥10%) treatment-emergent adverse events in all studies were central nervous system- and gastrointestinal-related, and included dizziness, headache, nausea, fatigue, ataxia, blurred vision, vomiting, diplopia, nystagmus and tremor. Adverse events (AEs) appeared to be dose-related and the incidence of AEs was generally higher during the Titration Phase than during the Maintenance Phase. Small, dose-related increases in the mean PR interval were observed in clinical trials. Asymptomatic first-degree atrioventricular (AV) block was observed as an adverse reaction in 0.4% of patients randomized to receive LCM and 0% of patients randomized to receive placebo. The percentage of subjects who completed the trial in SP667, SP754, and SP755 was 75%, 78.6%, and 83.6%, respectively. The reasons for discontinuation were similar across the trials. The most common reason for discontinuation in all 3 trials was AE (17% in SP667, 15.9% in SP754, and 9.2% in SP755). With the exception of discontinuation due to AEs, all other reasons for discontinuation occurred at a similar incidence across the 3 trials.

ii. Pooled Efficacy Analysis

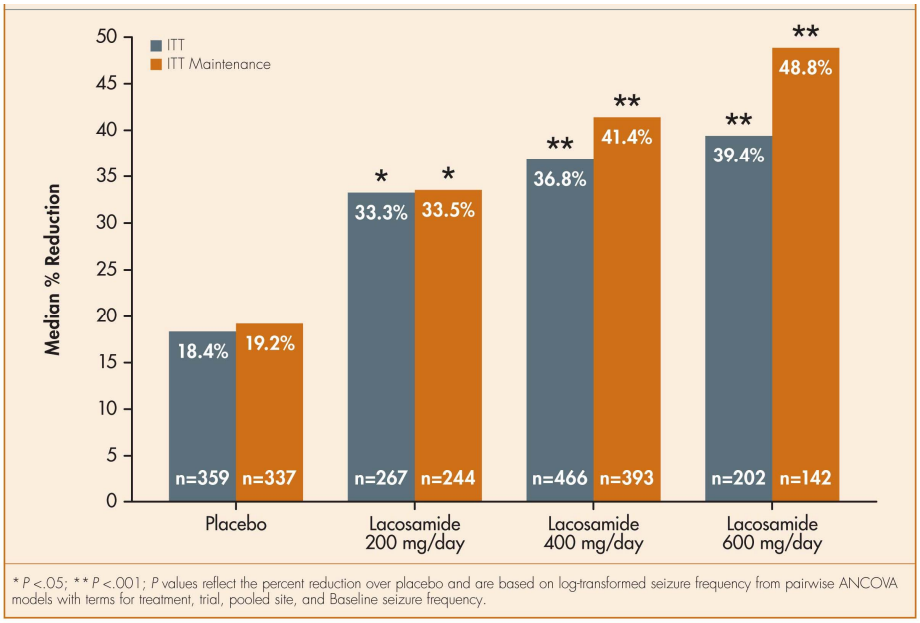
Chung et al (2008, Poster) [6] **analyzed pooled efficacy data from 3 Phase II/III trials (SP667 [LCM 200, 400, 600mg/day], SP754 [400, 600mg/day], and SP755 [200, 400mg/day]) by randomized dose**.

Trial designs were comparable with a 12-week fixed-dose maintenance phase, similar titration schedules (100 mg/day weekly increments), similar inclusion criteria, and matching primary efficacy endpoints. Similar trial designs allowed for a pooled analysis to be performed. Primary efficacy endpoints included the change in seizure frequency per 28 days from Baseline to Maintenance Phase and 50% responder rate (the percentage of subjects with ≥50% seizure reduction from Baseline to Maintenance phase). Pooled trial data were analyzed for the Intention to Treat (ITT) and Modified Intention to Treat (ITT Maintenance). ITT indicates all randomized subjects receiving ≥ 1 dose of trial medication with ≥ 1 post-baseline efficacy assessment. ITT Maintenance includes all ITT subjects, excluding those who dropped out during titration.

The data pool consisted of 1,294 treated subjects (placebo, n = 359; LCM 200 mg/day, n = 267; LCM 400 mg/day, n = 466; and LCM 600 mg/day, n = 202). At baseline, subjects were on average 38.6 years of age, and were primarily Caucasian. Subjects also reported > 2 to 3 times the number of seizures as required by inclusion criteria. The baseline seizure rate was high, and subjects reported more than 2 to 3 times the number of seizures required by the inclusion criteria. Baseline seizure rates ranged between 9.9 seizures per 28 days in the PBO group (SP755) to 16.5 seizures per 28 days in the LCM 600 mg/day treatment group (SP754). The majority of subjects (84%) were on 2 or 3 concomitant AEDs during the trials, mainly carbamazepine (35%), lamotrigine (31%), and levetiracetam (29%). A total of 88.3%, 82.8%, 77.9%, and 62.4% completed treatment for placebo, LCM 200, 400, and 600 mg/day groups. Overall, 77% of subjects had tried ≥4 lifetime antiepileptic drugs (AEDs) and 45% had tried ≥7 AEDs.

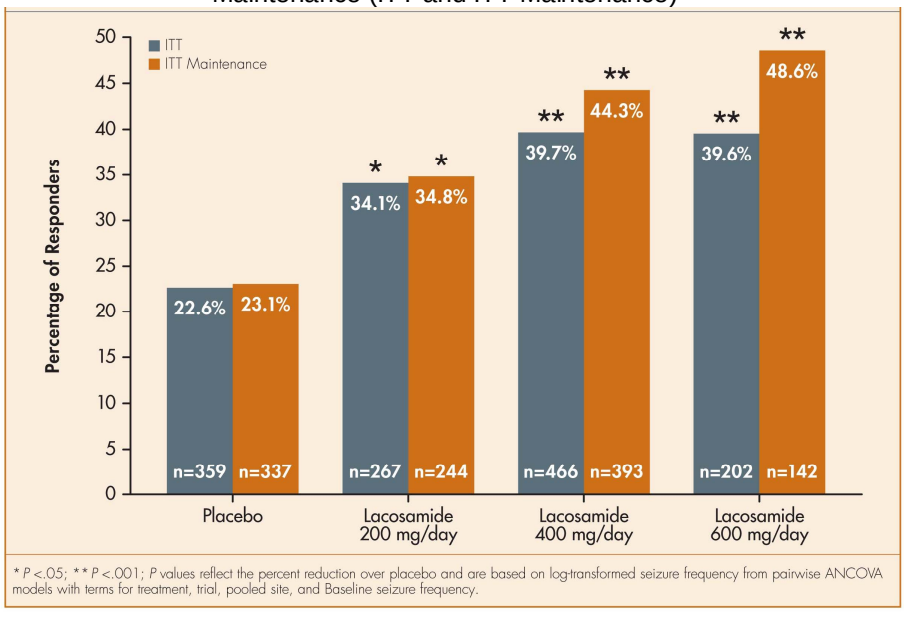
In this pooled analysis, LCM treatment resulted in statistically significant reductions in seizure frequency at all doses studied compared to PBO for both ITT and ITT maintenance groups. Likewise, all LCM treatment groups showed a significantly higher percentage of 50% responder rates for both ITT and ITT maintenance groups.

Figure 1: Pooled Results: Median Percentage Reduction in Seizure Frequency (Per 28 Days) from Baseline to Maintenance (ITT and ITT Maintenance) [6]



ITT: All randomized subjects receiving ≥1 dose of trial medication with ≥1 post-baseline efficacy assessment
ITT Maintenance: ITT subjects, excluding those who dropped out during titration

Figure 2: Pooled Results: Percentage of Subjects with Treatment Response ≥ 50% from Baseline to Maintenance (ITT and ITT Maintenance) [6]



ITT: All randomized subjects receiving ≥1 dose of trial medication with ≥1 post-baseline efficacy assessment
ITT Maintenance: ITT subjects, excluding those who dropped out during titration

References:

1. VIMPAT® [package insert]. Smyrna, GA: UCB; 2008.

2. Ben-Menachem E, Biton V, Jatuzis D, Abou-Khalil B, Doty P, Rudd GD. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. Epilepsia. 2007;48(7): 1308-17.
3. Chung S, Sperling M, Biton V, Krauss G, Beaman M, Hebert D. Lacosamide: Efficacy and Safety as Oral Adjunctive Treatment for Partial-Onset Seizures [abstract]. Neurology 70[11 Suppl 1], A74-A75. 2008.
4. Halasz P, Kalviainen R, Mazurkiewicz-Beldzinska M, Rosenow F, Sullivan T, Hebert D. Lacosamide: efficacy and safety as oral adjunctive therapy in adults with partial-onset seizures [abstract]. Eur J Neurol 2007;14(Suppl 1):209.
5. UCB Inc., Data on File.
6. Chung S, Rudd D, Hebert D, Doty P. Evaluation of Lacosamide Efficacy in Subjects with Partial-Onset Seizures Across the Dose Range Used in Phase II/III Clinical Trials. Poster presented at American Epilepsy Society 62nd Annual meeting; December 5-9, 2008; Seattle, WA.

VIMPAT® (lacosamide): SP667 - Epilepsy Pivotal Trials

Summary:

- VIMPAT® (lacosamide) (LCM) at doses of 400 mg/day and 600 mg/day produced a statistically significant reduction in seizure frequency (39% and 40%, respectively) versus placebo (PBO) (10%) for patients with partial-onset seizures, with or without secondary generalization, when used adjunctively with 1 or 2 concomitant AEDs.[2-4]
- The 50% responder rates for 400 mg/day (41%, p=0.0038) and 600 mg/day (38%, p=0.0141) were also statistically superior to placebo. [2-4]
- The LCM 400 mg/day dose was generally better tolerated than the 600 mg/day dose. [2-4]
- The most common treatment-emergent adverse events (TEAEs) included dizziness, headache, nausea, fatigue, ataxia, vision abnormal, vomiting, diplopia, somnolence and nystagmus. [2-4]
- LCM had no clinically relevant influence on ECG, laboratory, vital signs or body weight variables; however it did produce a small, dose-related increase in PR interval. [2-4]
- VIMPAT® (lacosamide) tablets are indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older. [1]
- VIMPAT® (lacosamide) injection is an alternative for patients when oral administration is temporarily not feasible.[1]

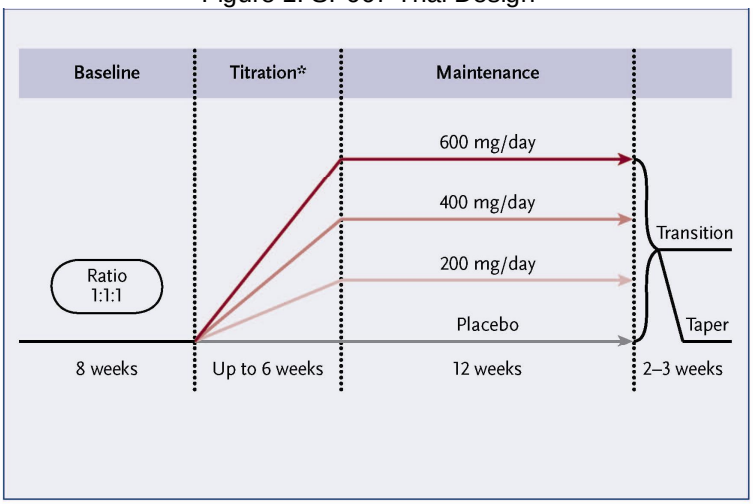
The package insert for VIMPAT® (lacosamide) contains information in the CLINICAL STUDIES section on this topic. Please review the enclosed full prescribing information.[1]

Ben-Menachem et al (2007) [2-4] **evaluated the efficacy and safety of adjunctive oral lacosamide in subjects using 1-2 antiepileptic drugs (AEDs) with uncontrolled partial onset seizures in a Phase II, multicenter, double-blind, placebo-controlled, 4-arm trial lasting 21 weeks.**

421 patients were randomized (1:1:1:1) to either placebo, lacosamide 200 mg/day, 400 mg/day or 600 mg/day in twice-daily dosing. Eligible patients must have had at least 4 partial-onset seizures (POS) during an 8-week baseline period, and must have POS for at least the last two years despite prior therapy with at least 2 AEDs. Baseline period was then followed by a 6-week titration period in which dosage was increased by 100 mg/day increments each week until the randomized dose of 200, 400, or 600 mg/day was attained for another 12 weeks. Patients who completed the maintenance period had the option to enter an open-label extension trial (SP615) by a blinded transition (2 weeks), or to taper and discontinue (3 weeks). Baseline characteristics between groups were similar. Approximately 84% of the patients were taking 2 AEDs, and the remainder were taking 1 AED when trial medication was added to their treatment regimen. Approximately 50% of patients had tried 7 or more AEDs in their lifetime. The most common (≥10%) concomitant AEDs in the trial population included carbamazepine (31%), levetiracetam (30%), lamotrigine (28%),

topiramate (20%), valproic acid (20%), oxcarbazepine (17%), and phenytoin (17%). The median baseline seizure frequency per 28 days was 11-13.

Figure 1: SP667 Trial Design [3]



Efficacy:

The primary efficacy assessment was seizure frequency, which was analyzed in 2 ways: 1) Reduction in seizure frequency per 28 days from Baseline to Maintenance Phase; and 2) Responder Rate, defined as a reduction of at least 50% in seizure frequency from Baseline to Maintenance Phase.

LCM 400 and 600 mg/day treatment groups were statistically superior to the placebo group in seizure frequency reduction at maintenance endpoint (400 mg/day, p= 0.0023; 600 mg/day p=0.0084). Even though the LCM 200 mg/day dose was not statistically significant, it demonstrated a numerically greater improvement in seizure frequency over placebo.

The 50% responder rates for LCM 400 mg/day (41%), and 600 mg/day (38%) were statistically superior to PBO (22%). Although the 50% responder rate for LCM 200 mg/day (33%) was not statistically significant, improved seizure frequency over PBO was demonstrated, warranting further study.

Table 1 – Median percent reduction in seizure frequency per 28 days at maintenance and 50% responder rate (FAS) [2,3]

Randomized Dose	N (efficacy analysis)	Median Percent Reduction in Seizure Frequency per 4 weeks at Maintenance (p-value vs placebo) †	50% Responder Rate at Maintenance (p-value vs placebo)	Seizure Freedom during Maintenance (%)
Placebo	96	10%	22%	0

LCM 200 mg/day	107	26%	33%	1%
LCM 400 mg/day	107	39%**	41%**	6%
LCM 600 mg/day	105	40%**	38%*	2%

* p < 0.05, ** p < 0.01, FAS – Full Analysis Set
† p-values reflect the percent reduction over placebo and are based on log-transformed data from pairwise treatment ANCOVA models

Table 2 – Median percent reduction in seizure frequency per 28 days at maintenance and 50% responder rate (PPS) [4]

Randomized Dose	N (efficacy analysis)	Median Percent Reduction in Seizure Frequency per 4 weeks at Maintenance (p-value vs placebo) †	50% Responder Rate at Maintenance (p-value vs placebo)	Seizure Freedom during Maintenance (%)
Placebo	85	12%	21%	0
LCM 200 mg/day	84	33%*	38%*	1%
LCM 400 mg/day	79	46%**	49%**	6%
LCM 600 mg/day	63	49%**	49%**	2%

* p < 0.05, ** p < 0.01, PPS – Per Protocol Set
† p-values reflect the percent reduction over placebo and are based on log-transformed data from pairwise treatment ANCOVA models

Secondary efficacy variables included the achievement of "seizure-free" status and proportion of seizure-free days during the maintenance phase. During the 12-week maintenance period, 7 patients were seizure free. Of these, patients were randomized to either LCM 200 mg/day (n=1), 400 mg/day (n=5), or 600 mg/day (n=1). The median change from baseline to end of maintenance phase in the percentage of seizure-free days was 3% for PBO, 6% for LCM 200 mg/day, 12% for LCM 400 mg/day and 600 mg/day. This change was statistically significant compared to placebo at the LCM 400 mg/day (p=0.0036) and LCM 600 mg/day (p=0.0004) groups.

Table 3: Statistical analysis for increase in percentage of seizure-free days over placebo at Maintenance endpoint (FAS) [4]

LCM treatment group	Treatment difference (SE)	p-value
200 mg/day	1.3 (2.28)	0.5656
400 mg/day	7.0 (2.36)	0.0036**
600 mg/day	8.9 (2.43)	0.0004**

**significant at the 0.0100 level
CI=confidence interval; LCM=lacosamide; SE=standard error

Safety:

Safety variables evaluated included adverse events, clinical laboratory assessments, ECGs, vital signs, and physical and neurological examinations. Eighty-four percent of LCM patients (270/321) experienced at least one treatment-emergent adverse event (TEAE) compared to 70% of PBO (68/97) during the treatment period; these events were mild to moderate in intensity. The most common TEAEs (≥10%) included dizziness, headache, nausea, fatigue,

ataxia, vision abnormal, vomiting, diplopia, somnolence and nystagmus. Of these, events that appeared to be dose-related included dizziness, nausea, fatigue, ataxia, vision abnormal, diplopia, vertigo, and nystagmus. The most common serious adverse events (SAEs) were dizziness and convulsions (n=3 each). Adverse events (AEs) tended to have an onset during the titration phase – this is the same phase where patients were more likely to discontinue treatment due to AEs. Discontinuations due to AEs tended to increase with higher doses of LCM. Evaluation of ECG data did not show a tendency for LCM to prolong the QT/QTc interval; there was a small, dose-related increase in the PR interval (4.2 msec at end of maintenance) in subjects taking LCM 400 mg/d.

References:

1. VIMPAT® [package insert]. Smyrna, GA: UCB; 2008.
2. Ben-Menachem E, Biton V, Jatuzis D, Abou-Khalil B, Doty P, Rudd GD. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. Epilepsia. 2007;48(7): 1308-17.
3. Ben Menachem E, Biton V, Jatuzis D, Abou-Khalil B, Doty P et al. Efficacy and safety of adjunctive oral lacosamide for the treatment of partial-onset seizures in patients with epilepsy. Poster presented at: 59th Annual Meeting of the American Epilepsy Society (AES), December 2-6, 2005; Washington, USA.
4. UCB Inc., Data on File. SP667.

VIMPAT® (lacosamide): SP754 - Epilepsy Pivotal Trials

Summary:

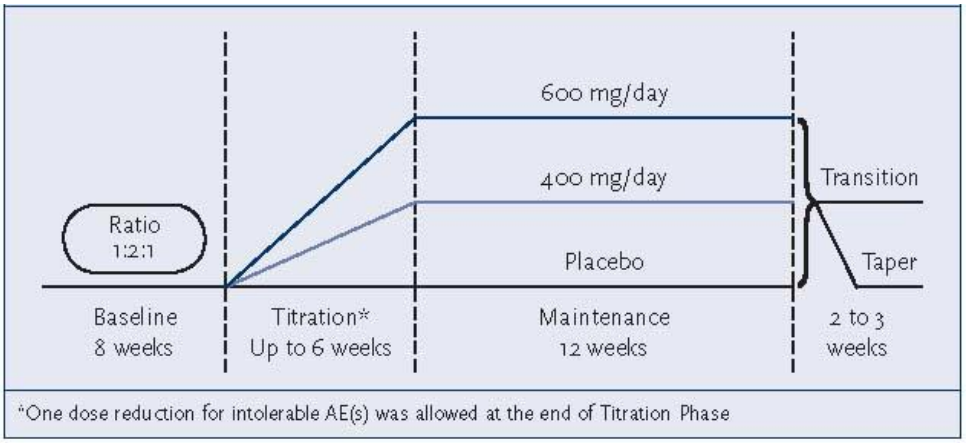
- This was a double-blind, placebo-controlled Phase 3 trial demonstrating that VIMPAT® (lacosamide) (LCM) at doses of 400 mg/day and 600 mg/day (200 and 300 mg bid, respectively) is an effective treatment when added to 1 to 3 approved concomitant AEDs in subjects experiencing uncontrolled partial seizures with or without secondary generalization. [2-4]
- The LCM 400 mg/day (37%%, p = 0.008) and 600 mg/day (38%, p = 0.006) treatment groups were statistically superior to the placebo (PBO) group (21%) in the reduction of seizure frequency per 28 days for the Maintenance Phase. [2-4]
- 50% responder rates for LCM 400 mg/day (38.3%) and 600 mg/day (41.2%) were also statistically superior to PBO (18.3%), where p<0.001. [2-4]
- LCM at 400 mg/day and 600 mg/day was generally well tolerated with dose-related adverse events (≥10% for lacosamide) including dizziness, nausea, diplopia, vision blurred, vomiting, and tremor . [2-4]
- LCM had no clinically relevant influence on ECG, laboratory, vital signs or body weight variables; however it did produce a small, dose-related increase in PR interval. [2-4]

The package insert for VIMPAT® (lacosamide) contains information in the CLINICAL STUDIES section on this topic. Please review the enclosed full prescribing information.[1]

Chung et al (2008, Abstract, Poster) [2-4] **investigated the efficacy and safety of VIMPAT (lacosamide) (LCM) 400 and 600 mg/day as adjunctive therapy in subjects with partial onset seizures (POS) with or without secondary generalization** and with or without vagal nerve stimulation (VNS). This was a Phase III, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial conducted in the US. 405 patients were randomized (1:2:1) to either placebo, LCM 400 mg/day or 600 mg/day of oral LCM given in 2 equally divided doses. Inclusion required subjects to have an average of ≥4 seizures per 28 days and no seizure-free period > 21 days in the 8-week period prior to baseline. Subjects must also be on a stable regimen of 1 to 3

antiepileptic drugs (AEDs) with or without additional vagal nerve stimulation. Concomitant AED doses and VNS settings were constant for a period of at least 4 weeks prior to entry at baseline. Titration occurred over 6 weeks, with weekly increments of LCM 100 mg/day until the randomized target dose. Target dose was maintained over 12 weeks, at which time patients were transitioned (2 weeks) to an open-label extension trial or tapered off the medication (3 weeks). Regarding concomitant AED use, 17.9%, 55.0%, and 27.1% of subjects were taking 1, 2, or 3 other AEDs, respectively, when LCM was added to their treatment regimen. Common (≥10%) concomitant AEDs used included levetiracetam (39%), lamotrigine (36%), carbamazepine (25%), oxcarbazepine (21%), phenytoin (19%), topiramate (18%), valproate (17%) and zonisamide (15%).

Figure 1: SP754 Trial Design [3]



Efficacy:

The primary efficacy variable was based on partial seizure frequency. Seizure frequency was analyzed in 2 ways: 1) Change in partial seizure frequency per 28 days from the Baseline Phase to the Maintenance Phase and 2) 50% responder rate, which is the proportion of responders where a responder is a subject experiencing ≥50% reduction in partial seizure frequency per 28 days from the Baseline Phase to the Maintenance Phase. A statistically significant median percent reduction in seizure frequency was observed in the LCM 400 mg/day (37%, p =

0.008) and 600 mg/day (38%, p = 0.006) groups compared to PBO (21%). Similarly, statistically significant differences in 50% responder rates vs PBO (18.3%) were seen in the LCM 400 mg/day (38.3%, p<0.001) and 600 mg/day (41.2%, p<0.001) groups.

Table 1 – Median percent reduction in seizure frequency per 28 days at maintenance and 50% responder rate (FAS) [2-4]

Randomized Dose	N (efficacy analysis)	Median Percent Reduction in Seizure Frequency per 4 weeks at Maintenance (p-value vs placebo) †	50% Responder Rate at Maintenance (p-value vs placebo)	Seizure Freedom during Maintenance n (%)
Placebo	104	21%	18%	0
LCM 400 mg/day	201	37%**	38%**	4 (2.5%)
LCM 600 mg/day	97	38%**	41%**	5 (8%)

* p < 0.05, ** p < 0.01, FAS – Full Analysis Set
† p-values reflect the percent reduction over placebo and are based on log-transformed data from pairwise treatment ANCOVA models

Table 2 – Median percent reduction in seizure frequency per 28 days at maintenance and 50% responder rate (PPS) [2-4]

Randomized Dose	N (efficacy analysis)	Median Percent Reduction in Seizure Frequency per 4 weeks at Maintenance (p-value vs placebo) †	50% Responder Rate at Maintenance (p-value vs placebo)	Seizure Freedom during Maintenance n (%)
Placebo	87	22%	18%	0
LCM 400 mg/day	140	40%*	40%**	4 (2.5%)
LCM 600 mg/day	53	50%**	51%**	4 (8%)

* p < 0.05, ** p < 0.01, PPS – Per Protocol Set
† p-values reflect the percent reduction over placebo and are based on log-transformed data from pairwise treatment ANCOVA models

Figure 2: Median Percent Reduction in Seizure Frequency per 28 Days from Baseline to Maintenance Phase (FAS) [3]

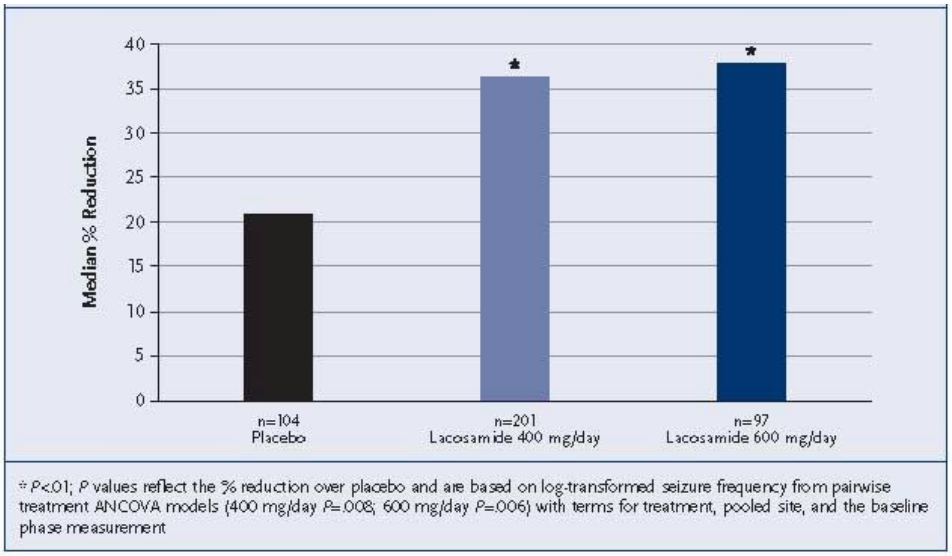
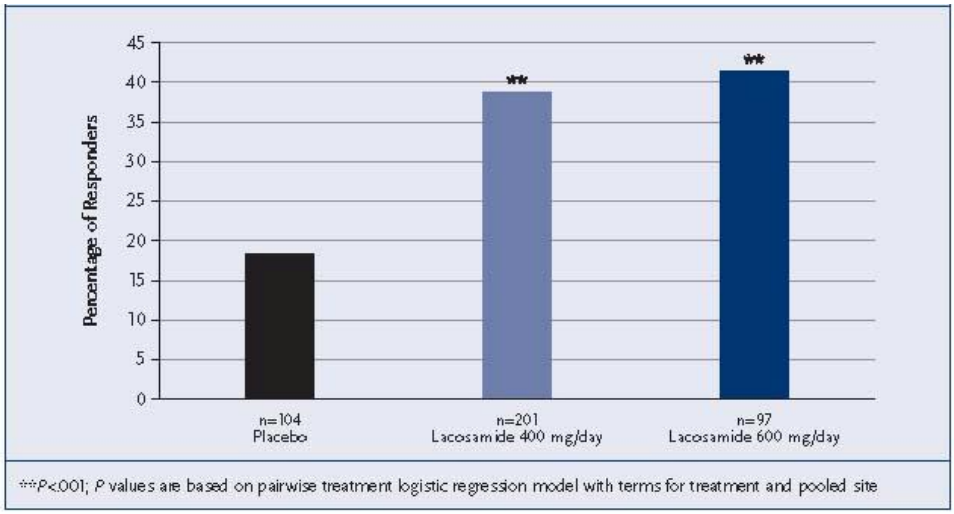


Figure 3: 50% Responder Rate from Baseline to Maintenance Phase (FAS) [3]



FAS = Full Analysis Set

Secondary efficacy variables included: 1) the proportion of seizure-free days during the Maintenance Phase for those who entered this Phase and 2) the proportion of subjects that completed the Maintenance Phase who achieved seizure-free status during this Phase. For subjects who completed the Maintenance Phase, 9 patients were seizure-free throughout the 12 week Maintenance Phase for LCM 400 mg/day (2.5%, 4/160), and LCM 600 mg/day (8.1%, 5/62). No PBO patients were seizure-free throughout the 12-week Maintenance Phase. Both the 400 mg/day and 600 mg/day LCM groups had significant and clinically relevant increases in the percentage of seizure-free days during the Maintenance Phase compared to placebo.

Table 3: Statistical analysis for increase in seizure-free days over placebo during the Maintenance Phase (FAS) [4]

LCM treatment group	Treatment difference (SE)	p-value
400mg/day	5.251 (2.10)	0.0130*
600mg/day	8.222 (2.22)	0.0003**

*significant at the 0.0500 level; **significant at the 0.0100 level
CI=confidence interval; LCM=lacosamide; SE=standard error
Note: Only subjects with Maintenance Phase data are included in this analysis.

Safety:

Across all treatment groups, the most common treatment-emergent adverse events (TEAEs) appeared to be associated with nervous system disorders and gastrointestinal events, and these were generally mild to moderate in intensity. TEAEs that appeared to be dose-related included diplopia, vision blurred, nausea, vomiting, dizziness, tremor, coordination abnormal, and nystagmus. The incidence of adverse events (AEs) leading to withdrawal tended to be higher in the Titration Phase as compared to the Maintenance Phase. Dizziness (9.3%) and coordination abnormal (2.0%) were the most common TEAEs leading to discontinuation in the Treatment Phase. LCM did not have any clinically relevant influence on ECG, laboratory, vital sign or body weight variables. There was a small dose-related increase in mean PR interval from Baseline among the LCM treatment groups vs PBO (1.2ms, 4.4ms, and 6.1ms for PBO, LCM 400 mg/day, 600 mg/day respectively).

References:

1. VIMPAT® [package insert]. Smyrna, GA: UCB; 2008.
2. Chung S, Sperling M, Biton V, Krauss G, Beaman M, Hebert D. Lacosamide: Efficacy and Safety as Oral Adjunctive Treatment for Partial-Onset Seizures [abstract]. Neurology 70[11 Suppl 1], A74-A75. 2008.
3. Chung S, Sperling M, Biton V, Krauss G, Beaman M, Hebert D. Lacosamide: Efficacy and Safety as Oral Adjunctive Treatment for Partial-Onset Seizures. Poster presented at: 60th Annual Meeting of the American Academy of Neurology (AAN); April 12-19, 2008; Chicago, USA.
4. UCB Inc., Data on File. SP754.

VIMPAT® (lacosamide): SP755 - Epilepsy Pivotal Trial

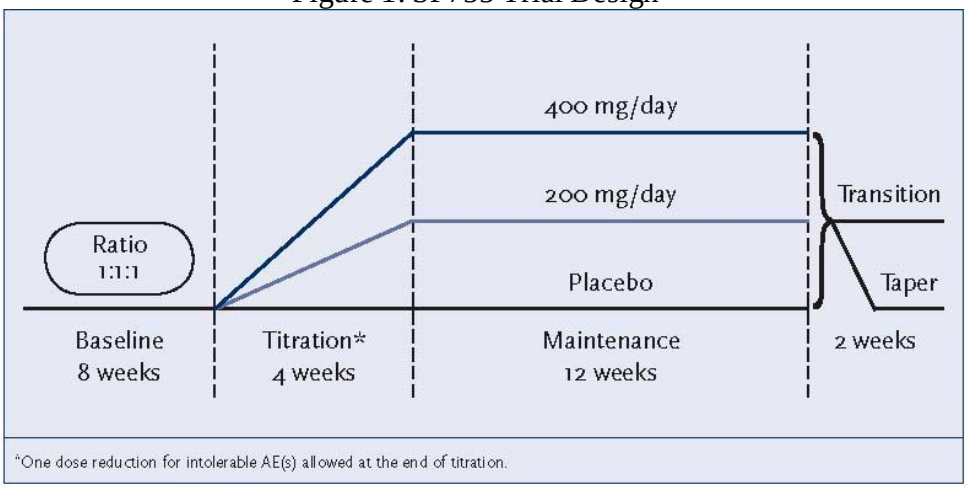
Summary:

- VIMPAT® (lacosamide) (LCM) at doses of 200 mg/day and 400 mg/day produced a statistically significant median reduction in seizure frequency (35.3% and 36.4%, respectively) over placebo (PBO) (20.5%) for patients with partial seizures when added to 1 to 3 approved concomitant AEDs in patients with epilepsy. [2-5]
- The 50% responder rate for LCM 400 mg/day (40.5%, $p<0.0063$) was statistically superior to PBO (25.8%), where $p<0.001$. [2-5]
- LCM at doses of 200 mg/day and 400 mg/day was generally better tolerated compared to placebo with the most common treatment-emergency adverse events (TEAEs) being dizziness, headache, diplopia, nausea and vertigo. [2-5]
- LCM had no clinically relevant influence on ECG, laboratory, vital signs or body weight variables; however it did produce a small, dose-related increase in PR interval. [2-5]
- VIMPAT® (lacosamide) tablets are indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older. [1]
- VIMPAT® (lacosamide) injection is an alternative for patients when oral administration is temporarily not feasible.[1]

The package insert for VIMPAT® (lacosamide) tablets contains information in the CLINICAL STUDIES section on this topic. Please review the enclosed full prescribing information.[1]

Halasz P. et al (2009, *Epilepsia In Press)* [2-5] **investigated the efficacy and safety of oral VIMPAT® (lacosamide) (LCM) 200 mg/day and 400 mg/day doses as administered concomitantly with 1-3 antiepiletic drugs (AEDs) in subjects with uncontrolled partial seizures** with or without secondary generalization. This was a Phase III, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial. 485 patients were randomized (1:1:1) in a double-blind fashion to either placebo (PBO), LCM 200 mg or 400 mg/day. At the end of the 8-week Baseline Phase, patients were titrated in weekly increments of 100mg/day to the randomized dose over 4 weeks, and maintained at the target dose for 12 weeks. After Maintenance Phase, subjects were either transitioned into an open-label extension trial or tapered off the medication over 2 weeks. To be included in the study, subjects had to have uncontrolled partial-onset seizures (POS) and were on a stable regimen of 1 to 3 concomitant antiepileptic drugs (AEDs) with or without vagal nerve stimulation (VNS). In this trial, 13%, 50% and 37% of subjects were taking 1, 2 or 3 other concomitant AEDs, respectively. Common (≥10%) concomitant AEDs used included carbamazepine (48%), valproate (33%), lamotrigine (31%), topiramate (28%), levetiracetam (20%), oxcarbazepine (16%), and clonazepam (11%).

Figure 1: SP755 Trial Design [3]



Efficacy:

The primary efficacy variable was the based on partial seizure frequency. Seizure frequency was analyzed in 2 ways: 1) Change in partial seizure frequency per 28 days from the Baseline Phase to the Maintenance Phase and 2) 50% responder rate, which is the proportion of responders where a responder is a subject experiencing ≥50% reduction in partial seizure frequency per 28 days from the Baseline Phase to the Maintenance Phase.

A statistically significant median percent reduction ($p<0.05$) in seizure frequency per 28 days from Baseline to Maintenance was observed in the LCM 200 mg/day (35%, $p = 0.02$) and 400 mg/day (36.0%, $p = 0.03$) treatment groups vs. PBO (21%). 50% responder rates for PBO (25.8%), LCM 200 mg/day (35%) and 400 mg/day (40.5%) indicated that the LCM groups were more likely than PBO to have 50% responders. However, only the LCM 400 mg/day was statistically significant at the $p<0.01$ level ($p<0.006$).

Table 1 – Median percent reduction in seizure frequency per 28 days at maintenance and 50% responder rate (FAS) [2-4]

Randomized Dose	N (efficacy analysis)	Median Percent Reduction in Seizure Frequency per 4 weeks at Maintenance (p-value vs placebo) †	50% Responder Rate at Maintenance (p-value vs placebo)	Seizure Freedom during Maintenance n (%)
Placebo	159	21%	26%	3 (2%)
LCM 200 mg/day	160	35%*	35%	5 (4%)
LCM 400 mg/day	158	36%*	40.5%**	3 (2%)

* p < 0.05, ** p < 0.01, FAS – Full Analysis Set
† p-values reflect the percent reduction over placebo and are based on log-transformed data from pairwise treatment ANCOVA models

Table 2 – Median percent reduction in seizure frequency per 28 days at maintenance and 50% responder rate (PPS) [2-4]

Randomized Dose	N (efficacy analysis)	Median Percent Reduction in Seizure Frequency per 4 weeks at Maintenance (p-value vs placebo) †	50% Responder Rate at Maintenance (p-value vs placebo)	Seizure Freedom during Maintenance n (%)
Placebo	138	25%	27.5%	3 (2%)
LCM 200 mg/day	140	35%*	35%	5 (4%)
LCM 400 mg/day	121	45%*	46%**	3 (2%)

* p < 0.05, ** p < 0.01, PPS – Per Protocol Set
† p-values reflect the percent reduction over placebo and are based on log-transformed data from pairwise treatment ANCOVA models

Figure 2: Median Percent Reduction in Seizure Frequency per 28 days from Baseline to Maintenance (FAS) [3]

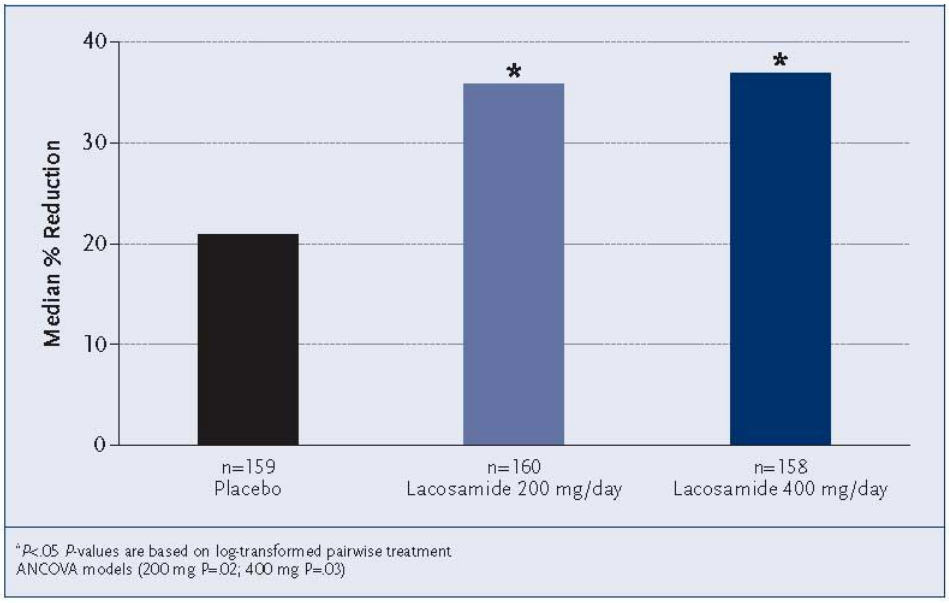
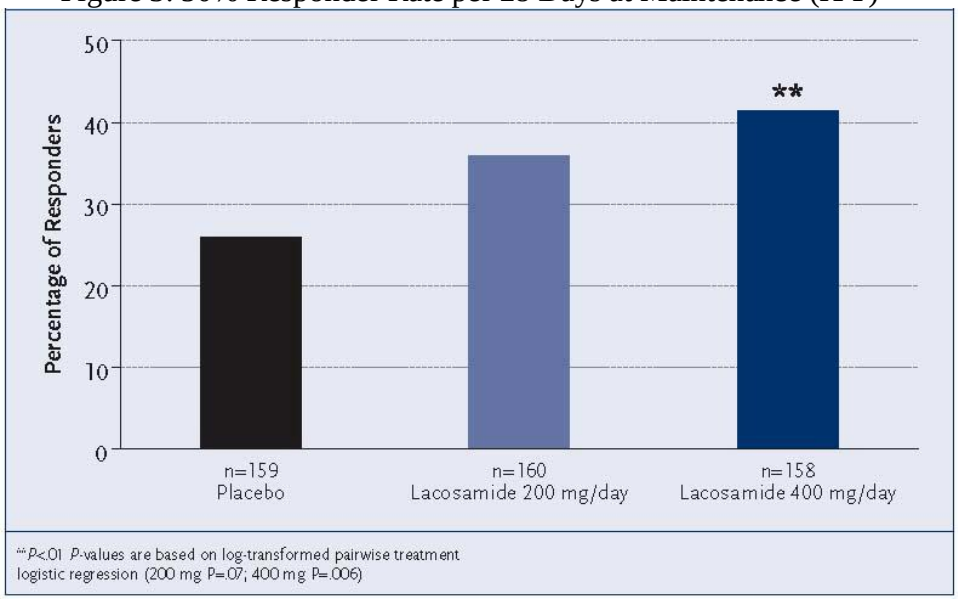


Figure 3: 50% Responder Rate per 28 Days at Maintenance (ITT) [3]



ITT = Intention to Treat

Secondary efficacy variables included: 1) the seizure-free status during the Maintenance Phase and 2) the proportion of seizure-free days during the Maintenance Phase (for subjects entering this phase). A statistically significant and clinically relevant increase in the percentage of seizure-free days during the Maintenance Phase was observed in the LCM 400 mg/day treatment group (5%) compared to PBO ($p < 0.01$). Although not statistically significant, LCM 200 mg/day showed an increase in the percentage of

seizure-free days over placebo. Throughout the 12-week Maintenance Phase, 11 patients were seizure-free: 5 subjects taking LCM 200 mg/day (3.6%), 3 subjects taking LCM 400 mg/day (2.4%) and 3 subjects taking PBO (2.1%).

Table 3: Statistical analysis for increase in seizure-free days over placebo during the Maintenance Phase (FAS) [4]

LCM treatment group	Treatment difference (SE)	p-value
200 mg/day	3.102 (1.61)	0.0550
400 mg/day	4.999 (1.77)	0.0052**

**significant at the 0.0100 level
CI=confidence interval; LCM=lacosamide; SE=standard error
Note: Only subjects with Maintenance Phase data are included in this analysis.

Safety:

Across all treatment groups, treatment-emergent adverse events (TEAEs) that were most common included central nervous system and gastrointestinal events. Notable adverse events (AEs) that appeared to be dose-related included dizziness, nausea, and vomiting, with most events being mild to moderate in intensity. 93.1%, 92.3%, and 92.7% of subjects experienced any AE in PBO, LCM 200 mg/day, and LCM 400mg/day treatment groups, respectively. For PBO and LCM 400 mg/day groups, the overall incidence of AEs was slightly higher during the Titration Phase than during the Maintenance Phase. The number of subjects who discontinued as a result of experiencing an AE was similar between PBO (5%) and LCM 200 mg/day groups (6%). The discontinuation rate was higher in the LCM 400 mg/day group (15%). Adverse events leading to discontinuation from the trial in at least 1% of patients across lacosamide treatment groups were diplopia (2.2%), vertigo (1.6%), vomiting(1.2%), and convulsion (1.2%).

There were no clinically relevant influences of LCM on ECG. A small dose-related increase in PR interval (4.6 ms for LCM 400 mg/day group) was observed. There were no reports of bundle branch block in any treatment group. This increase in PR interval did not affect the AE profile as only one lacosamide patient had ECG PR prolongation reported as an AE.

References:

1. VIMPAT® [package insert]. Smyrna, GA: UCB; 2008.
2. Halasz P, Kalviainen R, Mazurkiewicz-Beldzinska M, Rosenow, F, Doty, P, Hebert D, Sullivan T, on behalf of the SP755 Study Group. Adjunctive lacosamide for partial-onset seizures: efficacy and safety results from a randomized controlled trial. Epilepsia. In Press.
3. Halasz P, Kalviainen R, Mazurkiewicz-Beldzinska M, Rosenow F, Sullivan T, Hebert D. Lacosamide: efficacy and safety as oral adjunctive therapy in adults with partial-onset seizures [abstract]. Eur J Neurol 2007;14(Suppl 1):209.
4. Halasz P, Kalviainen R, Mazurkiewicz-Beldzinska M, Rosenow F, Sullivan T, Hebert D. Lacosamide: efficacy and safety as oral adjunctive therapy in adults with partial-onset seizures. Poster presented at 61st Annual Meeting of the American Epilepsy Society (AES); November 30 - December 4, 2007; Philadelphia, USA.
5. UCB Inc., Data on File. SP755

VIMPAT® (lacosamide): Open-Label Extension Trial (SP615) – Epilepsy

SUMMARY:

- SP615 (ClinicalTrials.gov Identifier: NCT00552305) is an open-label extension trial evaluating the long-term safety and efficacy of adjunctive oral VIMPAT® (lacosamide) (LCM) in patients with refractory partial-onset seizures. [4]
- VIMPAT® (lacosamide) tablets are indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older. [1]
- VIMPAT® (lacosamide) injection for intravenous use is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older when oral administration is temporarily not feasible. [1]
- This trial is on-going. An interim analysis of the data has been completed. [2-4]
- Data from the interim analysis support the long-term administration of open-label VIMPAT® as adjunctive therapy for partial-onset seizures. VIMPAT® was generally well tolerated and reduced seizure frequency. [2-4]
- The mean treatment duration was 724.4 days at the time of this interim analysis. The median modal dose of VIMPAT® across all subjects was 400 mg/day. [2-3,5]

The package insert for VIMPAT® (lacosamide) contains no information regarding long-term use for partial onset seizures. Please review the enclosed full prescribing information.[1]

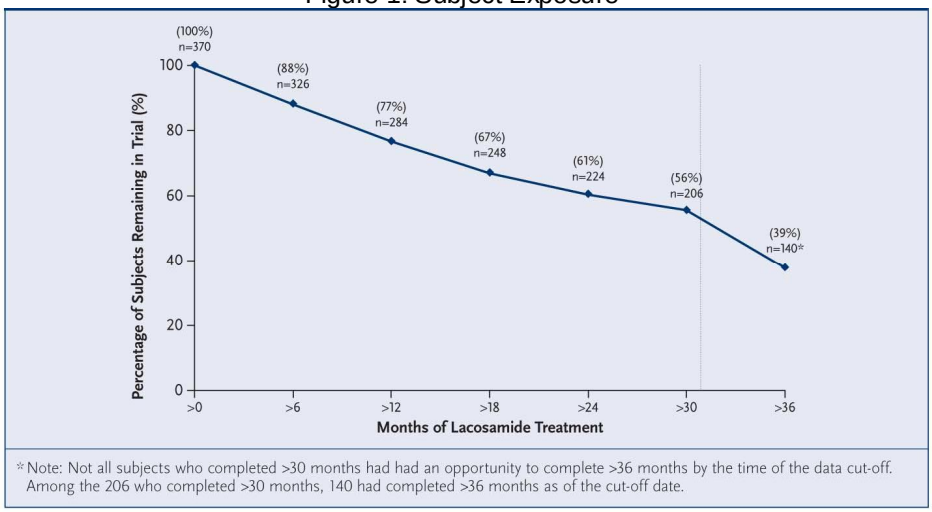
A literature search produced the following publication(s)

Rosenfeld et al (2007, Abstract) [2-5] **performed an interim evaluation of the long-term safety and efficacy of adjunctive oral VIMPAT® (lacosamide) (LCM) in patients with refractory partial-onset seizures (POS) who are on a stable regimen of anti-epileptic drugs (AEDs).**

This update provides an interim analysis of this Phase II, multicenter, multinational, open-label extension trial. Subjects who completed an initial parent Phase II trial (SP598, SP607, SP667) with LCM for the adjunctive treatment of POS were included. Subjects had received at least 1 dose of LCM. The main objectives of this trial were to analyze data on seizure reduction and maintenance of efficacy, along with safety information during long-term exposure of LCM. LCM dosing could be increased or decreased (100 mg/day per week) at the discretion of the investigator, with doses up to 800 mg/day (twice daily dosing) being used. Safety was evaluated through adverse events (AE), ECGs, vital signs, body weight and laboratory values. Efficacy was assessed based on the percent change from baseline in 28-day seizure frequency and response to treatment.

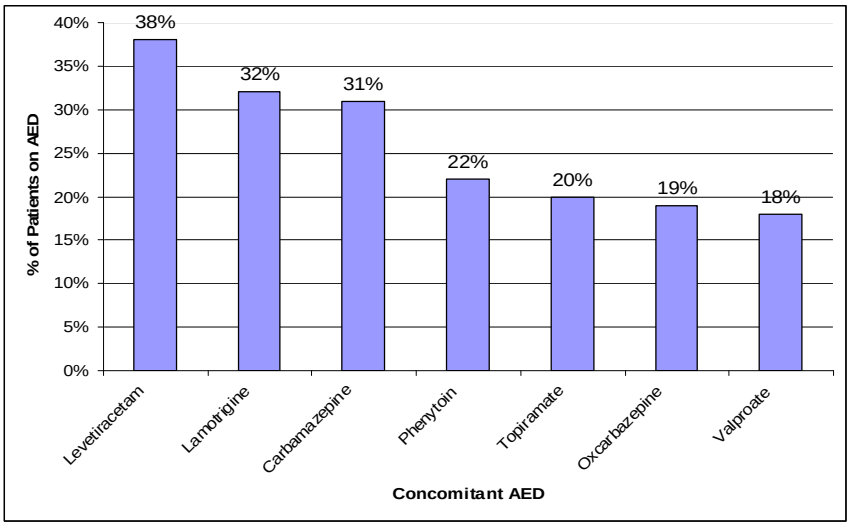
Of the 370 subjects enrolled, 284 (76.8%) subjects had > 12 months exposure to LCM, 224 (60.5%) subjects had >24 months exposure to LCM, and 140 (37.8%) subjects had 36 months exposure to LCM. At the time of this interim analysis, the mean treatment duration was 724.4 days. The median modal dose was 400 mg/day.

Figure 1: Subject Exposure [3]



The majority of patients had previously tried ≥7 antiepileptic drugs (AED) since being diagnosed with epilepsy (n = 192). A lesser number had previously tried 4-6 AEDs (n = 110). The most common concomitant AEDs (≥15% in total subjects) used in this trial included: levetiracetam (38%), lamotrigine (32%), carbamazepine (31%), phenytoin (22%), topiramate (20%), oxcarbazepine (19%), and valproate (18%).

Table 1: Concomitant AED Use [2]



Safety

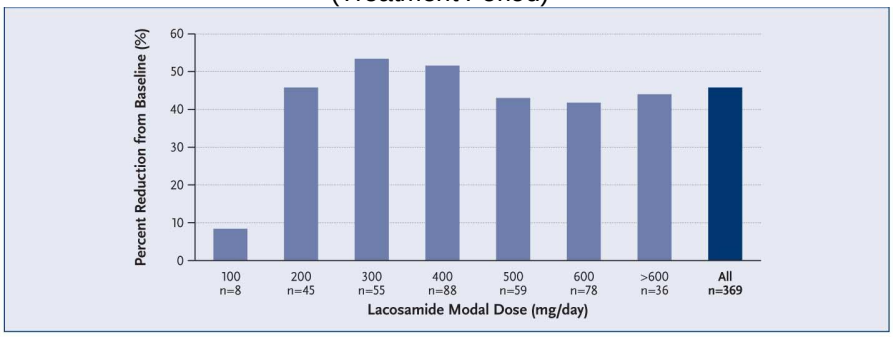
The most frequently reported treatment-emergent adverse events (TEAE) (≥10% of total population) were dizziness (37%), headache (18%), diplopia (14%), fatigue (14%), nasopharyngitis (14%), contusion (13%), coordination abnormal (13%), nausea (13%), Upper Respiratory Tract Infection (URTI) (13%), skin laceration (12%), vision blurred (12%), vomiting (12%) and sinusitis (10%). A total of 11.1% of subjects discontinued due to adverse

events (AEs); dizziness (1.6%) was the only AE that led to discontinuation in >1%. In general, the most common AEs were similar to those observed in double-blind trials; however, direct comparisons cannot be made due to differences in trials. Long-term LCM treatment was not associated with any change or pattern in vital signs, body weight or laboratory values. A small increase in median PR interval was observed.

Efficacy

The median percent reduction in seizure frequency across all treatment groups was 45.9%. In both 300 and 400 mg/day LCM groups (modal dose), a >50% reduction of seizure frequency per 28 days was achieved. The overall percentage of subjects with ≥50% response to LCM for the Treatment Period was 46.6%.

Figure 2: Median % Reduction from Baseline in Seizure Frequency per 28 Days by Modal Dose (Treatment Period) [3]



Data from this interim analysis support the long-term administration of open-label LCM as adjunctive therapy for POS.

REFERENCES:

1. VIMPAT® [package insert]. Smyrna, GA: UCB; 2009.
2. Rosenfeld W, Fountain NB, Kaubrys G, Heinzen L, McShea C. Lacosamide: an interim evaluation of long-term safety and efficacy as oral adjunctive therapy in subjects with partial-onset seizures [abstract]. Epilepsia 48[Suppl 6], 318-319. 2007.
3. Rosenfeld W, Fountain NB, Kaubrys G, Heinzen L, McShea C. Lacosamide: an interim evaluation of long-term safety and efficacy as oral adjunctive therapy in subjects with partial-onset seizures. Poster presented at 61st Annual Meeting of the American Epilepsy Society (AES); November 30 - December 4, 2007; Philadelphia, USA.
4. Clinical Trials.gov. Available at: http:///www.clinicaltrials.gov Accessed 7/18/2008
5. UCB Inc., Data on File. 2007.

VIMPAT® (lacosamide): Adverse Reactions and Safety Overview

SUMMARY:

- A post-hoc pooled analysis of the VIMPAT® (lacosamide) primary safety pool containing data from 3 pivotal, large-scale, randomized, double-blind, placebo-controlled partial onset seizure trials suggest that VIMPAT® is generally well tolerated when combined with up to three concomitant AEDs. [2-3]
    - The most common Treatment-Emergent Adverse Events (TEAEs) that occurred at an overall rate of ≥10% included dizziness, headache, nausea and diplopia. [1-3]
    - TEAEs were mild to moderate in intensity and generally dose-related. [1-3]
    - The incidence of TEAEs were lower during Maintenance phase compared to Titration for patients randomized to VIMPAT®. [2-3]
- *Discontinuation Rates*
    - In controlled clinical trials, the rate of discontinuation as a result of an adverse event was 8%, 17%, and 29% in patients receiving VIMPAT® doses of 200 mg, 400 mg, and 600 mg/day[†], respectively, and 5% in patients receiving placebo. [1]
    - The adverse events (AEs) most commonly (>1% in the VIMPAT® total group and greater than placebo) leading to discontinuation were dizziness, ataxia, vomiting, diplopia, nausea, vertigo, and vision blurred. [1]
- The recommended maintenance dose is 200 to 400 mg/day, based on individual patient response and tolerability. [1]
- In clinical trials, the 600 mg daily dose was not more effective than the 400 mg daily dose, and was associated with a substantially higher rate of adverse reactions.[1]

[†] The 600 mg/day dose is not FDA approved.

The package insert for VIMPAT® (lacosamide) contains information in the WARNINGS AND PRECAUTIONS, CLINICAL STUDIES and ADVERSE REACTIONS section on this topic. Please review the enclosed full prescribing information.[1]

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In all controlled and uncontrolled trials in patients with partial-onset seizures, 1327 patients have received VIMPAT of whom 1000 have been treated for longer than 6 months and 852 for longer than 12 months.

6.1 Clinical Trials Experience

Controlled Trials

Adverse reactions leading to discontinuation

In controlled clinical trials, the rate of discontinuation as a result of an adverse event was 8% and 17% in patients randomized to receive VIMPAT at the recommended doses of 200 and 400 mg/day, respectively, 29% at 600 mg/day, and 5% in patients randomized to receive placebo. The adverse events most commonly (>1% in the VIMPAT total group and greater than placebo) leading to discontinuation were dizziness, ataxia, vomiting, diplopia, nausea, vertigo, and vision blurred.

Most common adverse reactions

Table 2 gives the incidence of treatment-emergent adverse events that occurred in ≥2% of adult patients with partial-onset seizures in the total VIMPAT group and for which the incidence was greater than placebo. The majority of adverse events in the VIMPAT patients were reported with a maximum intensity of 'mild' or 'moderate'.

Table 2: Treatment-Emergent Adverse Event Incidence in Double-Blind, Placebo-Controlled Partial-Onset Seizure Trials (Events ≥2% of Patients in VIMPAT Total and More Frequent Than in the Placebo Group)

System Organ Class/ Preferred Term	Placebo N=364 %	VIMPAT 200 mg/day N=270 %	VIMPAT 400 mg/day N=471 %	VIMPAT 600 mg/day N=203 %	VIMPAT Total N=944 %
Ear and labyrinth disorder					
Vertigo	1	5	3	4	4
Eye disorders					
Diplopia	2	6	10	16	11
Vision blurred	3	2	9	16	8
Gastrointestinal disorders					
Nausea	4	7	11	17	11
Vomiting	3	6	9	16	9
Diarrhea	3	3	5	4	4
General disorders and administration site conditions					
Fatigue	6	7	7	15	9
Gait disturbance	<1	<1	2	4	2
Asthenia	1	2	2	4	2
Injury, poisoning and procedural complications					
Contusion	3	3	4	2	3
Skin laceration	2	2	3	3	3
Nervous system disorders					
Dizziness	8	16	30	53	31
Headache	9	11	14	12	13
Ataxia	2	4	7	15	8
Somnolence	5	5	8	8	7
Tremor	4	4	6	12	7
Nystagmus	4	2	5	10	5
Balance disorder	0	1	5	6	4
Memory impairment	2	1	2	6	2
Psychiatric disorders					
Depression	1	2	2	2	2
Skin and subcutaneous disorders					
Pruritus	1	3	2	3	2

Laboratory abnormalities

Abnormalities in liver function tests have been observed in controlled trials with VIMPAT in adult patients with partial-onset seizures who were taking 1 to 3 concomitant anti-epileptic drugs. Elevations of ALT to ≥3× ULN occurred in 0.7% (7/935) of VIMPAT patients and 0% (0/356) of placebo patients. One case of hepatitis with transaminases >20x ULN was observed in one healthy subject 10 days after VIMPAT treatment completion, along with nephritis (proteinuria and urine casts). Serologic studies were negative for viral hepatitis. Transaminases returned to normal within one month without specific treatment. At the time of

this event, bilirubin was normal. The hepatitis/nephritis was interpreted as a delayed hypersensitivity reaction to VIMPAT.

Other Adverse Reactions in Patients with Partial-Onset Seizures
The following is a list of treatment-emergent adverse events reported by patients treated with VIMPAT in all clinical trials in patients with partial-onset seizures, including controlled trials and long-term open-label extension trials. Events addressed in other tables or sections are not listed here. Events included in this list from the controlled trials occurred more frequently on drug than on placebo and were based on consideration of VIMPAT pharmacology, frequency above that expected in the population, seriousness, and likelihood of a relationship to VIMPAT. Events are further classified within system organ class.
Blood and lymphatic system disorders: neutropenia, anemia
Cardiac disorders: palpitations
Ear and labyrinth disorders: tinnitus
Gastrointestinal disorders: constipation, dyspepsia, dry mouth, oral hypoaesthesia General disorders and administration site conditions: irritability, pyrexia, feeling drunk
Injury, poisoning, and procedural complications: fall
Musculoskeletal and connective tissue disorders: muscle spasms
Nervous system disorders: paresthesia, cognitive disorder, hypoaesthesia, dysarthria, disturbance in attention, cerebellar syndrome
Psychiatric disorders: confusional state, mood altered, depressed mood

Intravenous Adverse Reactions
Adverse reactions with intravenous administration generally appeared similar to those observed with the oral formulation, although intravenous administration was associated with local adverse events such as injection site pain or discomfort (2.5%), irritation (1%), and erythema (0.5%). One case of profound bradycardia (26 bpm: BP 100/60 mmHg) was observed in a patient during a 15 minute infusion of 150mg VIMPAT. This patient was on a beta-blocker. Infusion was discontinued and the patient experienced a rapid recovery.

Comparison of Gender and Race
The overall adverse event rate was similar in male and female patients. Although there were few non-Caucasian patients, no differences in the incidences of adverse events compared to Caucasian patients were observed.

PARTIAL ONSET SEIZURE - PIVOTAL TRIALS

Biton et al (2008, Poster) [2-3,7] **summarized pooled safety data from 3 fixed-dose, randomized, double-blind, placebo-controlled, efficacy and safety Phase II/III clinical trials (SP667, SP754, SP755)** [4-6].

Patients were randomized in a fixed, forced titration scheme to either placebo, LCM 200 mg/day, 400 mg/day, or 600 mg/day[†] (SP667); to placebo, LCM 400 mg/day, or 600 mg/day (SP754); or to placebo, LCM 200 mg/day, or 400 mg/day (SP755; BID dosing for all LCM treatments). Eligible patients had at least 8 partial seizures (4 for SP667) during an 8-week baseline period, with no more than a 21-day seizure-free period. Concomitant antiepileptic drugs (AEDs) were kept stable in subjects with or without additional vagal nerve stimulation (VNS). Titration occurred over 6 weeks (4 weeks for SP755) in 100 mg/week increments, and patients were maintained at their randomized dosage for 12 weeks. After the 12-week maintenance phase, patients underwent either a 2 week transition into an open-label extension

trial or a 3 week taper off the study medication.(SP667, SP754). Patients enrolled in SP755 underwent a 2 week transition or taper after the maintenance phase. The majority of patients (78%) were exposed to LCM for at least 85 days. All subjects were receiving 1-3 concomitant antiepileptic drugs (AEDs), with 85% of LCM-randomized subjects receiving 2–3 concomitant AEDs.

Safety – Treatment Phase

Subjects receiving at least 1 dose of placebo or LCM treatment were included in this pooled safety assessment. The overall incidence of treatment-emergent adverse events (TEAEs) occurring in ≥ 10% of any group during the Treatment Phase (Titration + Maintenance) increased with increasing fixed doses of LCM (70%, 82% and 94% for 200 mg/day, 400 mg/day, and 600 mg/day respectively) compared to 65% (PBO).
The most frequently reported individual TEAEs (occurring in ≥ 10% of the total LCM group) compared to PBO were dizziness (31% vs 8%), headache (13% vs 9%), nausea (11% vs 4%) and diplopia (11% vs 2%). Dizziness, nausea and diplopia appeared to be dose-related, with the highest incidence in the 600 mg/day group. Nervous system and GI adverse events were the most common and appeared to be dose-related.

Subjects reported mild to moderate TEAEs. The incidence of severe TEAEs was 10.4% in the LCM-treatment groups compared to 4.7% in PBO. The most frequently reported severe common drug-associated TEAE was dizziness (3.7%), which occurred a higher incidence in subjects randomized to LCM 600 mg/day group (9.4%). The incidence of a severe TEAE of dizziness was similar in the LCM 200 mg/day (1.9%) and 400 mg/day (2.3%) groups.

Table 1: Treatment-Emergent Adverse Events occurring at a frequency ≥10% in any group during the Treatment Phase [2-3]

medDRA Preferred Term	Placebo (n = 364) n (%)	Lacosamide 200 mg/day (n = 270) n (%)	Lacosamide 400 mg/day (n = 471) n (%)	Lacosamide 600 mg/day (n = 203) n (%)	Total Lacosamide (n = 944) n (%)
Any Event	235 (65)	188 (70)	387 (82)	190 (94)	765 (81)
Dizziness	30 (8)	43 (16)	139 (30)	107 (53)	289 (31)
Headache	32 (9)	30 (11)	65 (14)	25 (12)	120 (13)
Nausea	16 (4)	20 (7)	53 (11)	35 (17)	108 (11)
Diplopia	7 (2)	17 (6)	49 (10)	33 (16)	99 (11)
Vomiting	9 (3)	16 (6)	40 (9)	32 (16)	88 (9)
Fatigue	21 (6)	19 (7)	34 (7)	30 (15)	83 (9)
Coordination Abnormal	6 (2)	11 (4)	34 (7)	31 (15)	76 (8)
Vision Blurred	9 (3)	6 (2)	40 (9)	33 (16)	79 (8)
Tremor	15 (4)	10 (4)	29 (6)	24 (12)	63 (7)
Nystagmus	14 (4)	6 (2)	21 (5)	21 (10)	48 (5)

Safety – Titration vs. Maintenance Phase

Overall, the incidence of TEAE was lower during the Maintenance compared to Titration for patients randomized to LCM. During the Titration Phase, dizziness was the only AE (25%)

that occurred at an incidence of ≥10% for those randomized to LCM, however in the Maintenance Phase, the dizziness was notably lower in the LCM group (8%).

Table 2: Incidence of common Treatment-Emergent Adverse Events during Titration compared to Maintenance Phase [2-3]

medDRA Preferred Term	TITRATION		MAINTENANCE	
	Placebo n = 364 (%)	Total Lacosamide n = 944 (%)	Placebo n = 337 (%)	Total Lacosamide n = 781 (%)
Dizziness	7	25	2	8
Headache	6	9	5	6
Nausea	4	9	1	3
Diplopia	1	9	1	3
Vomiting	2	8	1	4
Fatigue	5	8	1	2
Coordination Abnormal	1	7	<1	3
Vision Blurred	2	7	1	2
Tremor	3	5	1	2
Nystagmus	3	4	1	1

Safety – General

The incidence of weight gain, somnolence, cognitive and behavioral abnormalities appeared low. The occurrence of rash was similar between LCM (2% for 200 mg/day, 3% for 400 mg/day, 3% for 600mg) and PBO treatment groups (3%). Serious AEs occurred in 7% of LCM-treated patients compared to 4% of PBO patients. The serious AEs (≥1%) included dizziness (1.5% for LCM 600 mg/day vs 0% in all other groups), nystagmus (1% for LCM 600 mg/day vs 0% in all other groups) and convulsion (1.1%, 1.1%, 0% for LCM 200 mg/day, 400 mg/day and 600mg respectively, compared to 0.8% PBO). Across all LCM treatment groups, there were no clinically relevant changes on laboratory parameters, ECGs, vital signs, or body weight measurements. A small, dose-related increase in PR interval was observed.

Discontinuation Rates

The percentage of patients discontinuing treatment due to an AE was 5%, 8% 17%, and 29% for the PBO, LCM 200 mg/day, 400 mg/day and 600 mg/day groups respectively. The TEAE (>5%) leading to discontinuation in LCM-randomized subjects was dizziness and coordination abnormal (both were for the LCM 600 mg/day group). Discontinuation rates resulting from dizziness were <1% (LCM 200 mg/day), 4% (LCM 400 mg/day) and 17% (LCM 600 mg/day) compared to 1% (PBO). Discontinuation rates resulting from coordination abnormal were <1% (LCM 200 mg/day), 1% (LCM 400 mg/day), 5% (LCM 600 mg/day) compared to 0% (PBO).

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1. VIMPAT®[package insert]. Smyrna, GA: UCB; 2008.
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6. Halasz P, Kalviainen R, Mazurkiewicz-Beldzinska M, Rosenow F, Sullivan T, Hebert D. Lacosamide: efficacy and safety as oral adjunctive therapy in adults with partial-onset seizures [abstract]. Eur J Neurol 2007;14(Suppl 1):209.
7. UCB Inc., Data on File

VIMPAT® (lacosamide): IV – Clinical Trials

SUMMARY:

- SP616 and SP757 evaluated the safety, tolerability and pharmacokinetics of intravenous VIMPAT® (lacosamide) (IV LCM) [2-3]
- The safety profile for IV VIMPAT® infusion was comparable to oral VIMPAT® tablets based on analyses of adverse events (AEs), ECGs, vital signs, and laboratory values. [2-3]
- The pharmacokinetics and bioavailability of VIMPAT® following 30 and 60 minute infusions were similar to those after oral VIMPAT® with a slight increased value for C_{max} after the IV infusions. [2]
- Infusion site related AEs were infrequent and did not result in discontinuation of IV VIMPAT®. [2]
- Evaluation of ECG did not show any tendency for IV VIMPAT® to prolong the QT/QTc interval. However, a small increase in mean PR interval was observed in both IV and oral VIMPAT®. [2-3]
- IV VIMPAT® should be infused intravenously over a period of 30 to 60 minutes.[1]

The package insert for VIMPAT® (lacosamide) (LCM) contains more information in the CLINICAL STUDIES section on this topic. Please review the enclosed full prescribing information.[1]

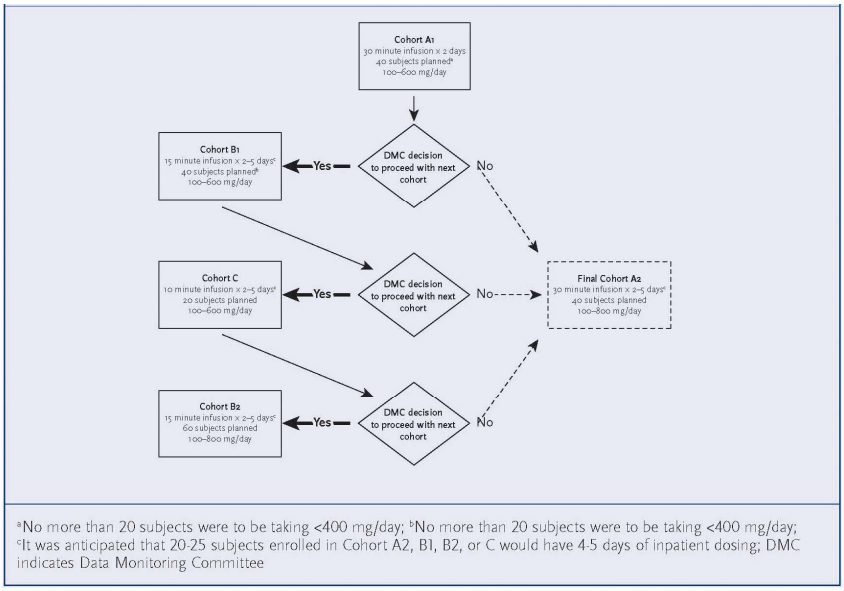
A literature search produced the following publication(s)

I. 10, 15, AND 30 MINUTE INTRAVENOUS INFUSIONS (SP757) [§ 3]

Krauss et al (2007, abstract) [3] **evaluated the safety, tolerability and pharmacokinetics of progressively shorter (I.V.) VIMPAT® (lacosamide) (LCM) infusions (30, 15, and 10 minutes) to determine the appropriate infusion duration for IV LCM as short-term replacement for oral LCM.**

This was a Phase III, multicenter, multinational, open-label, inpatient trial in which patients were enrolled from an open-label extension trial of oral LCM (SP615, SP756, or SP774) and already receiving stable doses of oral LCM (200-800 mg/day[†]) for at least 8 weeks. A total of 160 subjects were enrolled into 1 of 5 possible cohorts in this trial. A Data Monitoring Committee (DMC) reviewed safety data from each completed cohort prior to subsequent cohorts to determine which of the 5 pre-determined cohorts would be used. A maximum of 4 cohorts was possible, evaluating 3 different infusion durations (10, 15 or 30 minutes). Subjects entered into a 1-day Screening Phase followed by a Treatment Phase during which subjects received varying IV LCM infusions twice daily, instead of oral LCM. The dose of IV LCM was the same as that received in the open-label extension trial, and the duration of dosing was between 2-5 days depending on the cohort. A total of 160 patients were treated with IV LCM using 30- (n = 40), 15 – (n = 100), and 10- (n = 20) minute infusions.

Figure 1: Diagram of Study Design and Patient Cohorts [3]



[a]No more than 20 subjects were to be taking <400 mg/day; [b]No more than 20 subjects were to be taking <400 mg/day; [c]It was anticipated that 20-25 subjects enrolled in Cohort A2, B1, B2, or C would have 4-5 days of inpatient dosing; DMC indicates Data Monitoring Committee

Safety

157 subjects completed the trial; 3 discontinued prematurely from the 15 minute infusion group. In the 10-, 15- and 30-minute infusion duration groups, 35%, 24%, and 43% of subjects, respectively, reported ≥1 treatment- emergent adverse event (TEAE). Across all infusion duration groups, treatment-emergent adverse events (TEAEs) were most common in the nervous system disorders system organ class with headache (5-8%) and dizziness (5-8%) being the most commonly reported AEs. The incidence of AEs was comparable across all infusion groups, and AE frequency did not increase with shorter infusion durations or greater days of exposure. IV LCM was locally well tolerated as evidenced by few injection site reactions (0%, 2%, 0% across 10-, 15- and 30- minute infusions respectively). 4 subjects incorrectly received double their total IV LCM daily dose during the 30-minute infusion treatment period; 3 of these subjects did not report an AE, while 1 subject reported headache 30 minutes after evening infusion of 500mg (1000 mg/day). The headache resolved 1 hour later.

There was 1 serious adverse event (SAE) reported during the trial. This SAE of bradycardia occurred during a 15-minute infusion on Day 2 of IV LCM 150 mg bid (300 mg/day). The bradycardia resolved 4 minutes after onset, and did not occur with equivalent Day 1 infusions. Two independent cardiologists determined the event to be vasovagal in nature. The subject discontinued IV LCM and returned to the open-label extension trial.

Evaluation of ECG data from this trial did not show any tendency for IV LCM to prolong the QT/QTc interval. However, a small increase in mean PR interval was observed in all infusion duration groups.

Table 1: Incidence of AEs Reported for ≥2% of Subjects and ≥2 Subjects in Any Infusion Duration Group for All Days [3]

	Lacosamide Infusion Duration		
	10 minutes N = 20 n (%)	15 minutes N = 100 n (%)	30 minutes N = 40 n (%)
Headache	1 (5)	7 (7)	3 (8)
Dizziness	1 (5)	6 (6)	3 (8)
Diplopia	0 (0)	5 (5)	2 (5)
Somnolence	0 (0)	0 (0)	4 (10)
Nausea	1 (5)	1 (1)	2 (5)
Fatigue	1 (5)	2 (2)	0 (0)
Vision blurred	0 (0)	3 (3)	0 (0)
Abdominal pain upper	2 (10)	0 (0)	0 (0)
Constipation	0 (0)	2 (2)	0 (0)
Dry mouth	0 (0)	2 (2)	0 (0)
Injection site pain	0 (0)	2 (2)	0 (0)
WBC urine positive	0 (0)	0 (0)	2 (5)

Pharmacokinetics

Blood samples collected were analyzed for C_{max} and C_{trough}. Analysis of 3,000 individual pharmacokinetic samples showed that LCM plasma concentrations (C_{max} and C_{trough}) were similar across the 3 infusion duration groups for LCM at doses of 200-600mg/day. For all 3 infusion durations, LCM plasma concentrations increased proportionately as the actual daily dose increased.

† The 600 and 800 mg/day doses are not FDA approved.
§ The 10 and 15 minute intravenous infusions are not FDA approved.

II. 30 AND 60 MINUTE INTRAVENOUS INFUSIONS (SP616) [2,4]

Biton et al (2008) [2,4] **investigated the safety, tolerability and pharmacokinetics of intravenous VIMPAT® (lacosamide) (IV LCM) as replacement for oral LCM in patients with partial-onset seizures with or without secondary generalization over 3 days**.

This was a Phase II, multicenter, double-blind, double-dummy, randomized trial in which patients were enrolled from an ongoing open-label extension trial (SP615) and already receiving stable doses of oral LCM (200-600 mg/day†) for at least 8 weeks, along with a stable regimen of 1 or 2 antiepileptic drugs (AEDs). 60 patients were randomized (2:1) into IV LCM + oral PBO (BID) or IV PBO + oral LCM (BID). Patients were enrolled into 1 of 2 cohorts in a sequential manner, where the first 30 patients received 60-minute infusions of trial medication (Cohort A), and the next 30 patients received 30-minute infusions of trial

medication (Cohort B). Safety data from Cohort A were examined by a Data Monitoring Committee (DMC) prior to enrollment into Cohort B. Subjects entered a 1 day Screening Phase where they received a single infusion of IV PBO in a single-blind manner, followed by a 2 day Treatment Phase where they were given blinded trial medication BID at the equivalent dose of daily oral LCM (200-600 mg/day). End of Trial Phase assessments were done the next day after completion of Treatment Phase, and subjects resumed participation in the oral LCM open-label extension trial (SP615).

Safety

Safety evaluations included AEs, ECGs, vital signs, laboratory values, physical and neurological examinations and seizure counts. Fifty-nine of 60 patients completed the trial; 1 subject discontinued due to inability to gain vascular assess for pharmacokinetic sampling. 85% of subjects in Cohort A (60 min infusion) received doses ≥ 400 mg/day IV LCM; in Cohort B (30 min infusion), 68% of subjects received doses ≥ 400 mg/day IV LCM. Baseline characteristics were similar, with the majority of patients being female (58%) and Caucasian (88%). 27% (n=16) of patients experienced at least one treatment-emergent adverse event (TEAE) during the trial, with the frequency of TEAEs occurring at a higher rate in patients taking ≥400 mg/day (29%, 13/45) than in the patients taking <400mg/day (21%, 3/14) of oral or IV LCM. Injection site pain (during 1 of 4 infusions), dizziness, headache, back pain and somnolence were the only AEs reported by more than 1 subject. No subjects withdrew from the trial due to an AE. Mean ECG values (PR, QRS, QT and QTc) and vital signs were comparable among groups and no clinically significant changes in ECGs were reported. A small increase in mean PR interval in both IV and oral LCM was observed.

Table 2: Summary of Treatment-Emergent AEs Reported by 2 or More Subjects [4]

	Cohort A (60 min)		Cohort B (30 min)	
WHO-ART Preferred Term*	Oral LCM/ IV PBO (N=10) n (%)	IV LCM/ Oral PBO (N=20) n (%)	Oral LCM/ IV PBO (N=11) n (%)	IV LCM/ Oral PBO (N=19) n (%)
Injection Site Pain	0	0	0	2 (11)
Dizziness	0	1 (5)	0	2 (11)
Headache	0	2 (10)	1 (9)	0
Back Pain	0	2 (10)	0	0
Somnolence	0	0	0	2 (11)

*Subjects reporting the same preferred term more than once are counted once per preferred term.
Note: One subject receiving PBO infusion on Day -1 reported injection site pain.

Pharmacokinetics

Pharmacokinetic parameters that were derived from Day 2 plasma concentration data were AUC_{0-12}, C_{max}, C_{min}, t_{max} and $t_{½}$. Slightly increased values of C_{max} were observed after IV LCM compared to oral LCM. The t_{max} was reached earlier after IV infusions (30 minutes for 30-min infusion, 60 minutes for 60-min infusion) compared with oral LCM (2 hours). Ratios

of IV LCM to oral LCM for $AUC_{(0\text{-}12)norm}$ were near 100%, therefore bioavailability of IV LCM infusions was comparable to that after oral LCM. Sample sizes were too small ($n \leq 6$) to draw conclusions of the effect of IV LCM on plasma concentrations of concomitant AEDs. Results from this trial support further investigation of IV LCM given at shorter infusion durations.

† The 600 and 800 mg/day doses are not FDA approved.

References:

1. VIMPAT® [package insert]. Smyrna, GA: UCB; 2008.
2. Biton V, Rosenfeld WE, Whitesides J, Fountain NB, Vaiciene N, Rudd GD. Intravenous lacosamide as replacement for oral lacosamide in patients with partial-onset seizures. Epilepsia. 2008 Mar;49(3):418-24.
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